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Relationship of Vitamin D Deficiency to Echocardiographic Findings in Veterans

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Abstract

Objectives: Vitamin D deficiency has reached epidemic levels and has been frequently found in United States veterans. This deficiency has been linked to cardiovascular disease; however few studies have examined the relationship of vitamin D status to cardiac sonography. The purpose of the current study was to examine the relationship between vitamin D and echocardiography findings.

Design: Retrospective chart review.

Setting: Veterans administration hospital in the Southeastern United States. Participants: Thirty two eligible patients were included.

Measurements: Charts were reviewed for key variables of interest, and patients with coronary artery disease and without vitamin D testing were excluded.

Results: Several of the echocardiogram parameters were significantly associated with vitamin D level and status. Those with mitral regurgitation were more than twice as likely as remaining patients to be vitamin D deficient, as were those with pulmonary hypertension. In addition, patients with aortic sclerosis were almost twice as likely to be vitamin D deficient compared with patients who were negative.

Conclusion: Pending additional studies to confirm the cardiac benefits of a vitamin D repletes state, we urge clinicians to monitor and appropriately treat vitamin D deficiency. The benefits of maintaining adequate vitamin D reserves combined with the low potential for toxicity with modest vitamin D supplementation provides clinicians with a door to improving wellbeing and possibly ameliorating cardiac valvular disease.

Keywords: Vitamin D; Cardiovascular disease; Echocardiogram

Vitamin D deficiency has reached pandemic proportions [1]. The clinical relevance of the autocrine and paracrine effects of vitamin D is becoming increasingly evident [2]. Vitamin D deficiency has been linked to a number of cardiovascular abnormalities, including significant coronary stenoses in asymptomatic African American chronic cocaine users [3]. In addition, vitamin D deficiency independently predicts prevalence and development of coronary artery calcification in individuals with type 1 diabetes [4]. However, not all studies have found that a baseline 25(OH)D has prognostic value in secondary cardiovascular event incidence or mortality [5]. While using small doses of vitamin D may not result in any demonstrable cardiovascular benefit [6], severe vitamin D deficiency is significantly linked to sudden cardiac death, cardiovascular events and mortality [7].

Vitamin D may have multiple cardiac effects including direct effects on cardiac function. Vitamin D analogs have potent anti-hypertrophic cardiac activity in spontaneously hypertensive rats [8]. Echocardiographic evidence of left ventricular dysfunction in children with rickets has also been noted [9]. Vitamin D deficiency may be associated with myocardial dysfunction and death due to heart failure [10], and may also influence the cardiovascular system through effects on the renin aldosterone axis [11].

Few studies have examined the relationship between cardiac valvular function and vitamin D status. Moreover, the presence of coronary artery disease can significantly impact not only ejection fraction but also cardiac valvular function. We initiated the present study to determine if vitamin D was associated with poorer cardiac valvular function and pulmonary artery pressures in patients without documented coronary artery disease.

Methods

Participants and procedures

The study was conducted at a Veterans Administration Medical Center in the Southeastern United States. The Research and Development committee at the VA Medical Center and the Institutional Review Board at the affiliated university approved procedures and protocol. In addition, none of the authors had any conflicts of interest.

Patients without a diagnosis of coronary artery disease that had a documented 25(OH)D value and an echocardiogram were included. To ensure that vitamin D status would apply at the time of echocardiogram, only individuals with vitamin D testing and echocardiogram within a two week window were included. Data were obtained electronically

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through retrospective medical chart review. Echocardiogram data included parameters relating to left ventricular ejection fraction, left ventricular hypertrophy, diastolic dysfunction, mitral regurgitation, aortic sclerosis, aortic stenosis and pulmonary hypertension. Each parameter was sub-classified as absent, mild, moderate and severe.

During the study period 25, 802 echocardiograms were done at using Phillips Sono, model number 7500, and these were all interpreted by board certified cardiologists. During the study period, there were 180 echocardiograms done within two weeks of a vitamin D test. We reviewed 91 of these echocardiograms, and exclusion of patients with coronary artery disease reduced our final sample size to 32.

The presence and the grade of diastolic dysfunction were evaluated by using the Mitral Flow Velocities and the Mitral annulus velocities (determined by tissue Doppler). The severity of valvular abnormalities was determined according to the ASE guidelines (American Society of Echocardiography). Doppler, Color Flow imaging and Volumetric Method were used to quantify the severity of Mitral Regurgitation, regurgitant volume < 30 cc, regurgitant jet area less than 20% of the LA area, and regurgitant fraction less than 30% were considered as mild. Regurgitant volume > 60 cc, regurgitant jet area > 40% of the LA area and regurgitant fraction > 50% were considered severe. Vena contracta and effective regurgitant orifice were used at the discretion of the operator as is customary [12].

The Continuity Equation was used to evaluate the severity of Aortic Valve Stenosis, Aortic valve area > 1.5 CM2 was considered mild, area less than 1 CM2 was considered severe [13]. The modified Simpson method was used to calculate left ventricular Ejection Fraction, Tricuspid Regurgitation Velocity was used to calculate RVSP (Right Ventricular Systolic Pressure): 4 X Tricuspid regurgitation velocity^2 + Right atrial pressure.

Serum 25(OH)D was determined via immunochemiluminometric assay (Labcorp, Burlington, North Carolina). Vitamin D was examined as both a continuous and dichotomous variable with deficiency classified as 25(OH)D < 20 ng/ml [1].

Data analysis

Statistical analyses were performed using SPSS (SPSS Inc., version 14.0; Chicago, Illinois). All variables were checked for outliers and normality of distribution before analyses were performed. Correlations, logistic regressions, t-tests, and χ^2 analyses were used to answer the questions of interest. One tailed tests was used, due to a directional hypothesis and a small sample size, and a $p < 0.05$ was considered statistically significant.

Results

The final sample contained 32 patients. The vast majority were White (78%) and male (88%). The average age was 66 years, with a range from 43 to 88 years. Of the 32, 25% were diabetic, 69% had dyslipidemia, and 88% were hypertensive. The average BMI was 27.6, with a range from 16.9 to 41.7. The average vitamin D level for the sample was 26.5 with a range of 5.5 to 69.1. Using a cut-off value of 20, 43.8% of the patients would be considered Vitamin D deficient.

With respect to the echocardiogram, the average Left Ventricle Ejection Fracture (LVEF) was 53.9 (range 25-70). No diastolic dysfunction was evident for 69.3% of the patients (38.7% were Grade I). Mitral regurgitation was absent for 40.6% of patients (53.6% were mild, 3.1% were moderate), 40.6% were positive for aortic sclerosis. Aortic stenosis was absent for 93.8% (6.3% mild). Left ventricle hypertrophy was absent for 68.8% of patients (25.0% mild, 6.3% moderate). Finally, 71.0% did not have pulmonary hypertension (22.6% were mild, 6.5% were moderate, none were classified as severe).

The first question of interest addressed the association between vitamin D and LVEF. Treating both variables as continuous and calculating a correlation coefficient revealed a moderate correlation between the two variables, however due to the small sample size the association was not statistically significant (r=.203, p=.133). When vitamin D deficiency status was examined, the two groups (deficient and non-deficient) did not differ significantly in mean LVEF value (Deficient=52.50, Non-deficient=55.00, t=.76, p=.227).

Next examined were associations between vitamin D (level and deficiency status) and grade of the echocardiogram parameters. Because there were very few cases in the more severe categories, additional analyses were run collapsing some categories, as seen in Table 1. Several of the echocardiogram parameters were significantly associated with vitamin D level and status. Several other associations approached significance, and would likely be statistically significant with a larger sample size. Those with mitral regurgitation were more than twice as likely to be vitamin D deficient compared with those for whom this was absent. Those with aortic sclerosis were almost twice as likely to be vitamin D deficient compared with those who were negative. Finally, compared with those without pulmonary hypertension, those with any level of pulmonary hypertension had significantly lower levels of vitamin D and were more than twice as likely to be classified as vitamin D deficient.

Conclusions

The present study, to our knowledge, is the first to report an association between vitamin D status and pulmonary hypertension, mitral regurgitation and aortic sclerosis.

Ulrich et al. reported secondary hyperparathyroidism to be prevalent in pulmonary hypertension and postulated that vitamin D deficiency may contribute to both low bone mineral density and pulmonary hypertension, and serum parathyroid hormone elevation was likely due to vitamin D deficiency and was considerably higher in pulmonary hypertension than in left heart failure. Moreover, in patients on peritoneal dialysis, pulmonary hypertension is prevalent and pulmonary artery pressures correlate significantly with parathyroid hormone levels [15]. If vitamin D deficiency increases pulmonary arterial blood pressure, the mechanisms remain unknown. However it is known that vitamin D deficiency is common in patients with Anti-Phospholipid Antibody Syndrome (APS). This vitamin D deficiency is associated with clinically defined thrombotic events. One possibility is that vitamin D deficiency may lead to decreased inhibition of tissue factor expression and increased coagulation in APS [16]. Tissue factor expression has also been linked to experimental aortic valve sclerosis [17]. There is a strong relationship between serum concentrations of 25-hydroxy vitamin D and commonly used pulmonary function such as FEV1, and FVC [18]. It remains to be seen if ongoing diminished pulmonary function contributes to altered pulmonary artery pressures. No data have yet shown a decrease in pulmonary artery pressures with vitamin D supplementation.

Secondary elevation of parathyroid hormone has been linked to vascular calcification in renal failure [19]. In animal studies, parathyroid hormone replacement is associated with the development of intense aortic medial calcification and possibly coronary calcification [20]. The use of 22-oxacalcitriol in subtotally nephrectomized rats suppresses

	Vitamin D Level	p[a]	% Vitamin D Deficient	p[b]
Diastolic dysfunction				
Analyzed 3 Groups				
Absent	26.4	.459	42.1%	.334
Grade I	26.9		50.0%	
Grade II or III	-		-	
Mitral regurgitation				
Analyzed 3 Groups				
Absent	31.8	.118	23.1%	**.018**
Mild	23.0		55.6%	
Moderate or Severe	18.5		100.0%	
Analyzed 2 Groups				
Absent	28.4	.145	23.1%	**.024**
Mild, Moderate, Severe	22.3		57.9%	
Aortic sclerosis				
Negative	29.7	.069	31.6%	**.047**
Positive	21.7		61.5%	
Aortic Stenosis				
Analyzed 2 Groups				
Absent	25.9	.194	43.4%	.427
Mild, Moderate, or Severe	35.4		50.0%	
Left ventricle hypertrophy				
Analyzed 3 Groups				
Absent	28.4	.289	40.9%	.446
Mild	22.2		50.0%	
Moderate or Severe	22.5		50.0%	
Analyzed 2 Groups				
Absent	28.4	.145	40.9%	.316
Mild, Moderate, Severe	22.3		50.0%	
Pulmonary Hypertension				
Absent	30.5	**.014**	31.8%	**.037**
Mild, Moderate, Severe	17.8		66.7%	

p[a] values (one-tailed) correspond to t or F values
p[b] values (one-tailed) correspond to chi-square values

Table 1: Associations between Vitamin D Level and Status and Echocardiogram Parameters.

parathyroid hormone and is associated with less risk of cardiovascular calcification [21]. Parathyroid hormone (PTH) related peptide has also been linked to vascular calcification through autocrine/paracrine mechanisms [22] and its expression may be regulated by vitamin D [23]. In patients with primary hyperparathyroidism the data support an association between low vitamin D levels and the development of left ventricular hypertrophy [24].

Clinical studies also show a link between hypovitaminosis D and mitral ring calcification [25]. It remains to be seen if this calcification plays a role in mitral valvular dysfunction. There is some evidence that valvular calcification can worsen cardiac hypertrophy in patients on peritoneal dialysis [26]. Calcific aortic stenosis is the most frequently acquired valvular disease of the elderly in the Western world, with significant association of vitamin D receptor polymorphism and calcific aortic valve stenosis [27]. Parathyroid hormone gene variation is one of the few positive associations noted in calcific aortic stenosis [28]. However, vitamin D may have a bimodal relationship with calcific aortic stenosis since in animal studies extremely large doses have been associated with induction of calcific aortic stenosis [29-31]. In vitro studies suggest that valvular calcification can lead to impaired diastolic function with prolongation of closing times and higher closing volume [32]. In end stage renal disease, after adjustment for BP and age, 25(OH)D(3) and 1,25(OH)(2)D(3) were negatively correlated with aortic pulse wave velocity ($P < 0.001$) and positively correlated with Brachial artery distensibility [33]. Aortic sclerosis may be associated with increased thrombotic risk [34] and the proinflammatory profile seen with Vitamin D deficiency may contribute to this risk [35]. In hemodialysis patients, oral cholecalciferol supplementation allows attenuation of inflammation [36].

While calcification and cardiac valvular malfunction have been assumed to be part of the aging process, data suggest that vitamin D deficiency either directly or indirectly via increased parathyroid hormone levels may promote valvular calcification [37]. Vitamin D replacement may reduce deleterious effects of parathyroid hormone on cardiac function [38]. Parathyroid hormone predicted hospitalization due to heart failure even after accounting for established risk factors [39].

While the case for vitamin D replacement in heart failure remains controversial, at least one study indicates that serum 25(OH)D is associated with functional capacity in elderly patients with heart failure [40]. Moreover, an improvement in ejection fraction in African Americans with treatment of vitamin D deficiency and secondary hyperparathyroidism was noted [41]. In renal failure, observational studies indicate that vitamin D treatment maybe associated with a significant reduction of cardiovascular death among dialysis patients and a reduction in left ventricular hypertrophy [42].

The strength of the present study comes from exclusion of

patients with coronary artery disease and the link found between echocardiographic parameters and vitamin D. Like all studies of this type, it has flaws inherent in retrospective data analyses including the possibility of a selection bias. Further, restricting the sample to those without coronary artery disease (less than half of those who had an echocardiogram) and those with vitamin D testing within two weeks of the echocardiogram (only a small percentage of those who had echocardiograms) was necessary based on the study hypotheses. However, the resultant small sample size decreased statistical power, precluding the identification of small effects, and making it possible the study group was not representative of all veterans. We also cannot exclude the possibility that other factors (i.e., hypertension, diabetes and chronic kidney disease) may have contributed to the findings reported here. However, the current sample size precluded accounting for such variables.

Vitamin D testing and monitoring remains suboptimal in the veteran's population [43]. The recent Institute of Medicine report [IOM] [44] may lead to reduced testing and the failure of this report to account for the existence of subgroups at high risk of profound vitamin D deficiency is a major flaw leading to significant criticism [45]. However, the more recent position paper from the Endocrine society acknowledges the high prevalence of Vitamin D deficiency and the need for using larger doses of vitamin D than recommended by the IOM [46]. This report is more in line with emerging studies suggesting hypovitaminosis D is an independent risk factor for all-cause and cardiovascular mortality [47]. We recommend that clinicians consider testing and treating vitamin D deficiency more intensively in their patients with cardiac valvular disease. Though no studies to date have demonstrated that vitamin D supplementation will prevent progression of the echocardiographic findings, such treatment has a low risk of toxicity and can be done at a minimal cost. Additional prospective studies with large number of patients may clarify the relationship.

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